

General

Guideline Title

2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis.

Bibliographic Source(s)

Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, Moreland LW, O'Dell J, Winthrop KL, Beukelman T, Bridges SL Jr, Chatham WW, Paulus HE, Suarez-Almazor M, Bombardier C, Dougados M, Khanna D, King CM, Leong AL, Matteson EL, Schousboe JT, Moynihan E, Kolba KS, Jain A, Volkman ER, Agrawal H, Bae S, Mudano AS, Patkar NM, Saag KG. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2012 May;64(5):625-39. [45 references] [PubMed](#)

Guideline Status

Note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary.

Recommendations

Major Recommendations

Note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary. The recommendations that follow are based on the previous version of the guideline.

The levels of evidence supporting the recommendations (A-C) are defined at the end of the "Major Recommendations" field.

Recommendations for the Use of Disease-Modifying Antirheumatic Drugs (DMARDs) and Biologic Agents in Patients Who Qualify for Treatment of Rheumatoid Arthritis (RA)

This 2012 American College of Rheumatology (ACR) recommendations update incorporates the evidence from systematic literature review synthesis and recommendations from 2008 and rates updated and new clinical scenarios regarding the use of DMARDs and biologic agents for the treatment of RA. Terms used in the recommendations are defined in Table 2 of the original guideline document. The 2012 recommendations are listed in the 4 sections below and in the following order:

1. Indications for and switching DMARDs and biologic agents: early RA (indications, see Figure 1 in the original guideline document) followed by established RA (indications and switching, see Figure 2 in the original guideline document), along with details of the level of evidence supporting these recommendations (see Supplementary Appendix 7, available in the online version at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658))
2. Use of biologic agents in patients with hepatitis, malignancy, or congestive heart failure (CHF) who qualify for RA management (see Table 4 in the original guideline document)

3. Screening for tuberculosis (TB) in patients starting or currently receiving biologic agents as part of their RA therapy (see Figure 3 in the original guideline document)
4. Vaccination in patients starting or currently receiving DMARDs or biologic agents as part of their RA therapy (see Table 5 in the original guideline document)

The recommendations in the text below and in Tables 4 and 5 in the original guideline document represent the results of the 2012 update only, whereas Figures 1–3 in the original guideline document also incorporate some of the 2008 ACR RA recommendations that did not change. Areas of uncertainty by the panel (that did not lead to recommendations) are noted in Supplementary Appendix 8 (available in the online version of this article at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658)).

1. Indications for Starting, Resuming, Adding, or Switching DMARDs or Biologic Agents

The panel first describes a recommendation targeting remission or low disease activity in RA (section 1A). This is followed by recommendations for DMARD or biologic agent use in early RA (section 1B). Next, the panel provides recommendations for initiating and switching between DMARDs and biologic agents in established RA (section 1C).

1A. Target Low Disease Activity or Remission

The panel recommends targeting either low disease activity (see Table 3 in the original guideline document) or remission (see Table 2 in the original guideline document) in all patients with early RA (see Figure 1 in the original guideline document; level of evidence C) and established RA (see Figure 2 in the original guideline document; level of evidence C) receiving any DMARD or biologic agent.

1B. Early RA (Disease Duration <6 Months)

In patients with early RA, the panel recommends the use of DMARD monotherapy both for low disease activity and for moderate or high disease activity with the absence of poor prognostic features (see Figure 1 in the original guideline document; level of evidence A–C) (details are shown in Supplementary Appendix 7, available in the online version of this article at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658)).

In patients with early RA, the panel recommends the use of DMARD combination therapy (including double and triple therapy) in patients with moderate or high disease activity plus poor prognostic features (see Figure 1 in the original guideline document; level of evidence A–C).

In patients with early RA, the panel also recommends the use of an anti-tumor necrosis factor (anti-TNF) biologic with or without methotrexate in patients who have high disease activity with poor prognostic features (see Figure 1 in the original guideline document; level of evidence A and B). Infliximab is the only exception and the recommendation is to use it in combination with methotrexate, but not as monotherapy.

1C. Established RA (Disease Duration ≥6 Months or Meeting the 1987 ACR RA Classification Criteria)

The remainder of panel recommendations regarding indications for DMARDs and biologic agents are for patients with established RA. The 3 subsections below define recommendations for initiating and switching therapies in established RA (see Figure 2 in the original guideline document). Where the prognosis is not mentioned, the recommendation to use/switch to a DMARD or a biologic agent applies to all patients, regardless of prognostic features.

Initiating and Switching Among DMARDs

If after 3 months of DMARD monotherapy (in patients without poor prognostic features), a patient deteriorates from low to moderate/high disease activity, then methotrexate, hydroxychloroquine, or leflunomide should be added (see rectangle A of Figure 2 in the original guideline document; level of evidence A and B).

If after 3 months of methotrexate or methotrexate/DMARD combination, a patient still has moderate or high disease activity, then add another non-methotrexate DMARD or switch to a different non-methotrexate DMARD (see rectangle B of Figure 2 in the original guideline document; level of evidence B and C).

Switching from DMARDs to Biologic Agents

If a patient has moderate or high disease activity after 3 months of methotrexate monotherapy or DMARD combination therapy, as an alternative to the DMARD recommendation just noted above, the panel recommends adding or switching to an anti-TNF biologic, abatacept, or rituximab (see rectangles C and D of Figure 2 in the original guideline document; level of evidence A–C).

If after 3 months of intensified DMARD combination therapy or after a second DMARD, a patient still has moderate or high disease

activity, add or switch to an anti-TNF biologic (see rectangle C of Figure 2 in the original guideline document; level of evidence C).

Switching Among Biologic Agents Due to Lack of Benefit or Loss of Benefit

If a patient still has moderate or high disease activity after 3 months of anti-TNF biologic therapy and this is due to a lack or loss of benefit, switching to another anti-TNF biologic or a non-TNF biologic is recommended (see rectangles F and G of Figure 2 in the original guideline document; level of evidence B and C).

If a patient still has moderate or high disease activity after 6 months of a non-TNF biologic and the failure is due to a lack or loss of benefit, switch to another non-TNF biologic or an anti-TNF biologic (see rectangles F and G of Figure 2 in the original guideline document; level of evidence B and C). An assessment period of 6 months was chosen rather than 3 months, due to the anticipation that a longer time may be required for efficacy of a non-TNF biologic.

Switching Among Biologic Agents Due to Harms/Adverse Events

If a patient has high disease activity after failing an anti-TNF biologic because of a serious adverse event, switch to a non-TNF biologic (see rectangle E of Figure 2 in the original guideline document; level of evidence C).

If a patient has moderate or high disease activity after failing an anti-TNF biologic because of a nonserious adverse event, switch to another anti-TNF biologic or a non-TNF biologic (see rectangle F of Figure 2 in the original guideline document; level of evidence B and C).

If a patient has moderate or high disease activity after failing a non-TNF biologic because of an adverse event (serious or nonserious), switch to another non-TNF biologic or an anti-TNF biologic (see rectangle F of Figure 2 in the original guideline document; level of evidence C).

2. Use of Biologic Agents in RA Patients With Hepatitis, Malignancy, or Chronic Heart Failure (CHF), Qualifying for More Aggressive Treatment (level of evidence C for all recommendations)

Hepatitis B or C

The panel recommends that etanercept could potentially be used in RA patients with hepatitis C requiring RA treatment (see Table 4 in the original guideline document).

The panel also recommends not using biologic agents in RA patients with untreated chronic hepatitis B (disease not treated due to contraindications to treatment or intolerable adverse events) and in RA patients with treated chronic hepatitis B with Child-Pugh class B and higher (see Table 4 in the original guideline document; for details of Child-Pugh classification, see Table 2 in the original guideline document). The panel did not make recommendations regarding the use of any biologic agent for treatment in RA patients with a history of hepatitis B and a positive hepatitis B core antibody.

Malignancies

For patients who have been treated for solid malignancies more than 5 years ago or who have been treated for nonmelanoma skin cancer more than 5 years ago, the panel recommends starting or resuming any biologic agent if those patients would otherwise qualify for this RA management strategy (see Table 4 in the original guideline document).

The panel only recommends starting or resuming rituximab in RA patients with: 1) a previously treated solid malignancy within the last 5 years, 2) a previously treated nonmelanoma skin cancer within the last 5 years, 3) a previously treated melanoma skin cancer, or 4) a previously treated lymphoproliferative malignancy. Little is known about the effects of biologic therapy in patients with a history of a solid cancer within the past 5 years owing to the exclusion of such patients from participation in clinical trials and the lack of studies examining the risk of recurrent cancer in this subgroup of patients.

CHF

The panel recommends not using an anti-TNF biologic in RA patients with CHF that is New York Heart Association (NYHA) class III or IV and who have an ejection fraction of 50% or less (see Table 4 in the original guideline document).

3. TB Screening for Biologic Agents (level of evidence C for all recommendations except for initiation of biologic agents in patients being treated for latent TB infection [LTBI], where the level of evidence is B)

The panel recommends screening to identify LTBI in all RA patients being considered for therapy with biologic agents, regardless of the presence of risk factors for LTBI (see diamond A of Figure 3 in the original guideline document). It recommends that clinicians assess the patient's medical history to identify risk factors for TB (specified by the Centers for Disease Control and Prevention [CDC]) (see Table 2 in

the original guideline document).

The panel recommends the tuberculin skin test (TST) or interferon-gamma–release assays (IGRAs) as the initial test in all RA patients starting biologic agents, regardless of risk factors for LTBI (see diamond A of Figure 3 in the original guideline document). It recommends the use of the IGRA over the TST in patients who had previously received a bacillus Calmette-Guerin (BCG) vaccination, due to the high false-positive test rates for TST (see Figure 3 in the original guideline document).

The panel recommends that RA patients with a positive initial or repeat TST or IGRA should have a chest radiograph and, if suggestive of active TB, a subsequent sputum examination to check for the presence of active TB (see diamonds B and C of Figure 3 in the original guideline document). RA patients with a negative screening TST or IGRA may not need further evaluation in the absence of risk factors and/or clinical suspicion for TB. Since patients with RA may have false-negative TST or IGRA results due to immunosuppression, a negative TST or IGRA should not be interpreted as excluding the possibility that a patient has LTBI. Accordingly, in immunosuppressed RA patients with risk factors for LTBI and negative initial screening tests, the panel recommends that a repeat TST or IGRA could be considered 1–3 weeks after the initial negative screening (see diamond A of Figure 3 in the original guideline document).

If the RA patient has active or latent TB based on the test results, the panel recommends appropriate antitubercular treatment and consideration of referral to a specialist. Treatment with biologic agents can be initiated or resumed after 1 month of latent TB treatment with antitubercular medications and after completion of the treatment of active TB, as applicable (see Figure 3 in the original guideline document).

The panel recommends annual testing in RA patients who live, travel, or work in situations where TB exposure is likely while they continue treatment with biologic agents (see diamond D of Figure 3 in the original guideline document). Patients who test positive for TST or IGRA at baseline can remain positive for these tests even after successful treatment of TB. These patients need monitoring for clinical signs and symptoms of recurrent TB, since repeating tests will not help in the diagnosis of recurrent TB.

4. Vaccination in Patients Starting or Currently Receiving DMARDs or Biologic Agents as Part of Their RA Therapy (level of evidence C for all recommendations)

The panel recommends that all killed (pneumococcal, influenza intramuscular, and hepatitis B), recombinant (human papillomavirus [HPV] vaccine for cervical cancer), and live attenuated (herpes zoster) vaccinations should be undertaken before starting a DMARD or a biologic agent (see Table 5 in the original guideline document).

It also recommends that, if not previously done, vaccination with indicated pneumococcal (killed), influenza intramuscular (killed), hepatitis B (killed), and HPV vaccine (recombinant) should be undertaken in RA patients already taking a DMARD or a biologic agent (see Table 5 in the original guideline document).

The panel recommends vaccination with herpes zoster vaccine in RA patients already taking a DMARD. All vaccines should be given based on age and risk, and physicians should refer to vaccine instructions and CDC recommendations for details about dosing and timing issues related to vaccinations.

Definitions:

Level of Evidence

- Level of Evidence A: Data derived from multiple randomized clinical trials.
- Level of Evidence B: Data derived from a single randomized trial, or nonrandomized studies.
- Level of Evidence C: Only consensus opinion of experts, case studies, or standard-of-care.

Note: Level C evidence often denoted a circumstance where medical literature addressed the general topic under discussion but it did not address the specific clinical situations or scenarios reviewed by the panel.

Clinical Algorithm(s)

Clinical algorithms are provided in the original guideline document for the following:

- 2012 American College of Rheumatology (ACR) recommendations update for the treatment of early rheumatoid arthritis (RA), defined as a disease duration <6 months
- 2012 ACR recommendations update for the treatment of established RA, defined as a disease duration ≥6 months or meeting the 1987 ACR classification criteria
- 2012 ACR recommendations update for tuberculosis (TB) screening with biologic agent use

Scope

Disease/Condition(s)

Rheumatoid arthritis

Guideline Category

Evaluation

Management

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Rheumatology

Intended Users

Physicians

Guideline Objective(s)

- To simplify the treatment algorithms for patients with rheumatoid arthritis (RA) and providers
- To provide clinicians with choices for treatments of patients with active RA, both in early and established disease phases
- To provide guidance regarding treatment choices in RA patients with comorbidities such as hepatitis, congestive heart failure (CHF), and malignancy

Target Population

Patients with rheumatoid arthritis

Interventions and Practices Considered

1. Nonbiologic disease-modifying antirheumatic drug (DMARD) therapy
 - Leflunomide or methotrexate
 - Hydroxychloroquine or minocycline
 - Sulfasalazine
 - Dual-DMARD combinations
 - Triple-DMARD combinations
2. Biologic DMARDs
 - Anti-tumor necrosis factor alpha (TNF α) agents
 - Non-TNF α agents (abatacept, rituximab, tocilizumab)
3. Safety monitoring, risk surveillance, and preventive immunizations
4. Tuberculosis screening for patients receiving biologic DMARDs

Note: The use of biologic therapy combinations was considered but not recommended.

Major Outcomes Considered

- Change in the level of disease activity
- Percent of patients who attain remission
- Adverse effects of treatment
- Degree of preservation of physical function
- Incidence of work-related disability
- Health-related quality of life

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Systematic Literature Review: Sources, Databases, and Domains

Literature searches for both disease-modifying antirheumatic drugs (DMARDs) and biologic agents relied predominantly on PubMed searches with medical subject headings and relevant keywords similar to those used for the 2008 American College of Rheumatology (ACR) rheumatoid arthritis (RA) recommendations (see Supplementary Appendices 1 and 2, available in the online version at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658)). The working group included randomized controlled trials (RCTs), controlled clinical trials, quasi-experiment designs, cohort studies (prospective or retrospective), and case-control studies, with no restrictions on sample size. More details about inclusion criteria are listed below and in Supplementary Appendix 3 (available in the online version at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658)).

The 2008 recommendations were based on a literature search that ended on February 14, 2007. The literature search end date for the 2012 update was February 26, 2010 for the efficacy and safety studies and September 22, 2010 for additional qualitative reviews related to tuberculosis (TB) screening, immunization, and hepatitis (similar to the 2008 methodology). Studies published subsequent to that date were not included.

For biologic agents, the working group also reviewed the Cochrane systematic reviews and overviews (published and in press) in the Cochrane Database of Systematic Reviews to identify additional studies and further supplemented by hand checking the bibliographies of all included articles. Finally, the Core Expert Panel (CEP) and the Task Force Panel (TFP) confirmed that the relevant literature was included in the evidence synthesis. Unless they were identified by the literature search and met the article inclusion criteria (see Supplementary Appendix 3, available in the online version at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658)), the panel did not review any unpublished data from product manufacturers, investigators, or the Food and Drug Administration (FDA) Adverse Event Reporting System.

The working group searched the literature for the 8 DMARDs and 9 biologic agents most commonly used for the treatment of RA. Literature was searched for 8 DMARDs: azathioprine, cyclosporine, hydroxychloroquine, leflunomide, methotrexate, minocycline, organic gold compounds, and sulfasalazine. Similar to 2008, azathioprine, cyclosporine, and gold were not included in the recommendations based on their infrequent use and lack of new data (see Table 1 in the original guideline document). Literature was searched for 9 biologic agents: abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, and tocilizumab. Anakinra was not included in the recommendations due to infrequent use and lack of new data. Details of the bibliographic search strategy are listed in Supplementary Appendix 1 (available in the online version at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658)).

Literature Search Criteria and Article Selection

Inclusion and Exclusion Criteria for Review of Article Abstracts and Titles

With the exception of assessment of TB, hepatitis, and vaccination (see below), studies were included if they met all of the following criteria: 1)

original study in English language with an abstract, 2) observational studies (case-control or cohort) or intervention studies, 3) related to the treatment of RA with DMARDs or biologic agents, and 4) study duration of at least 6 months (see Supplementary Appendix 2, available in the online version at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658)).

Studies were excluded if they met any of the following criteria: 1) the report was a meeting abstract, review article, or meta-analysis; 2) the study duration was less than 6 months; and 3) DMARDs or biologic agents were used for non-RA conditions (e.g., psoriatic arthritis, systemic lupus erythematosus) or non-FDA-approved use in health conditions other than RA (e.g., biologic agents in vasculitis) (see Supplementary Appendix 2, available in the online version at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658)).

Selection Criteria for Articles Reviewing Efficacy/Adverse Events

Two reviewers independently screened the titles and abstracts of the 2,497 potential articles from the PubMed and Cochrane Library searches by applying the above selection method. Any disagreements were resolved by consultation with the lead reviewer. The lead author also reviewed all titles and abstracts to identify any that might have been overlooked. The working group identified 149 original articles from the 3 searches for full-text retrieval. After excluding duplicates, 128 unique original articles were identified and the data were abstracted. This included 16 articles focused on DMARDs and 112 on biologic agents (98 on the 6 biologic agents assessed in the 2008 RA recommendations and 14 on certolizumab pegol, golimumab, and tocilizumab, 3 newer biologic agents that had been added since the 2008 recommendations) (see Supplementary Appendix 3, available in the online version at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658)). A list of all included articles is provided in Supplementary Appendix 4 (available in the online version at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658)).

Additional Literature Searches for Articles Reviewing TB Screening, Hepatitis, and Vaccination

Qualitative reviews of the literature were performed for these 3 topics (completed September 22, 2010). Similar to the strategy for the 2008 recommendations, literature searches were broadened to include case reports and case series of any size, review articles, and meta-analyses, plus inclusion of diseases other than RA. In addition, the developer included searches on the Centers for Disease Control and Prevention (CDC) web site (www.cdc.gov) for past and current recommendations regarding TB screening and vaccination in immunocompromised patients.

PubMed Search Strategy for DMARDs

The following limits* were placed on all searches: English, Human, ages 13 to 18 years, and all adults 19+ years. Subsequently, the terms "rheumatoid arthritis and X" were entered with X being one of eight drugs or drug combinations noted below.

- Methotrexate
- Sulfasalazine
- Minocycline
- Leflunomide
- Hydroxychloroquine
- Gold
- Azathioprine
- Cyclosporine

PubMed Search Strategy for Biologics Included in 2008 Recommendations

The entry term of 'rheumatoid arthritis' was combined with the intervention terms for domains 1 (indications for use) and 4 (assessing clinical response). Within domain 2 (screening for TB), the entry term 'tuberculosis' was combined with the intervention terms. For domain 3 (monitoring of side-effects), the entry terms 'contraindications', 'adverse effects', 'drug monitoring', and 'complications' were combined with the intervention terms.

PubMed Search Strategy for Three New Biologics Not Included in 2008 Recommendations

The entry term of 'rheumatoid arthritis' was combined with the intervention terms for domains 1 (indications for use) and 4 (assessing clinical response). Within domain 2 (screening for TB), the entry term 'tuberculosis' was combined with the intervention terms. For domain 3 (monitoring of side-effects), the entry terms 'contraindications', 'adverse effects', 'drug monitoring', and 'complications' were combined with the intervention terms.

Agreement Between Reviewers for Selection of Studies for Full-Text Retrieval

The kappa coefficients (agreement beyond chance) for independent selection of articles for full-text review by the 2 reviewers met or exceeded 0.60 (good) for DMARDs, 0.65 (very good) for the 6 biologic agents included in the 2008 ACR recommendations, and 0.84 (excellent) for a combination of certolizumab pegol, golimumab, and tocilizumab.

Number of Source Documents

Disease-modifying anti-rheumatic drugs (DMARDs): 16

Biologics included in 2008 recommendations: 98

Biologics not included in 2008 recommendations: 14

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Level of Evidence

- Level of Evidence A: Data derived from multiple randomized clinical trials
- Level of Evidence B: Data derived from a single randomized trial, or nonrandomized studies
- Level of Evidence C: Only consensus opinion of experts, case studies, or standard-of-care

Note: Level C evidence often denoted a circumstance where medical literature addressed the general topic under discussion but it did not address the specific clinical situations or scenarios reviewed by the panel.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Full-Text Article Review, Data Abstraction, Data Entry, and Evidence Report Generation

The full text of each article was reviewed; data abstraction and entry were performed by reviewers using a standardized Microsoft Access database that was developed and used for data abstraction for the 2008 American College of Rheumatology (ACR) rheumatoid arthritis (RA) recommendations. Two reviewers were assigned to abstract data on disease-modifying antirheumatic drugs (DMARDs), rituximab, and the rest of the biologic agents. To ensure that the error rates were low and abstractions were similar, 26 articles related to biologic agents were dually abstracted by 2 abstractors. The data entry errors were less than 3%. Entered data were further checked against raw data on biologic agents from the Cochrane systematic reviews. Following this comprehensive literature review, the developers developed an evidence report using the data abstracted from the published studies.

Methods Used to Formulate the Recommendations

Expert Consensus (Delphi)

Description of Methods Used to Formulate the Recommendations

The guideline developer utilized the same methodology as described in detail in the 2008 guidelines to maintain consistency and to allow cumulative

evidence to inform this 2012 recommendations update. These recommendations were developed by 2 expert panels: 1) a nonvoting working group and Core Expert Panel (CEP) of clinicians and methodologists responsible for the selection of the relevant topic areas to be considered, the systematic literature review, the evidence synthesis, and creation of "clinical scenarios"; and 2) a Task Force Panel (TFP) of 11 internationally recognized expert clinicians, patient representatives, and methodologists with expertise in rheumatoid arthritis (RA) treatment, evidence-based medicine, and patient preferences who were tasked with rating the scenarios created using an ordinal scale specified in the RAND/University of California at Los Angeles (RAND/UCLA) Appropriateness Method. This method solicited formal input from this multidisciplinary TFP to make recommendations informed by the evidence.

Development of Clinical Scenarios

Clinical scenarios were drafted by the investigators and the Core Expert Panel (CEP), based on the updated evidence report. The developers used the same key determinant clinical thresholds and treatment decision branch points that were developed for the 2008 American College of Rheumatology (ACR) RA treatment recommendations. Clinical scenarios were constructed based on permutations in the particular therapeutic considerations that reflected: 1) disease duration (early versus established RA), 2) disease activity (low, moderate, or high) (Tables 2 and 3 and Supplementary Appendix 5, available in the online version at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658)), 3) current medication regimen, and 4) presence of poor prognostic factors (yes or no, as defined in the 2008 ACR recommendations). An example of a clinical scenario is: "The patient has active established RA and has failed an adequate trial of an anti-tumor necrosis factor (anti-TNF) biologic because of adverse events. Is it appropriate to switch to another anti-TNF biologic after failing etanercept?" (see Supplementary Appendix 6, available in the online version at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2151-4658](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658)). Scenarios included both new considerations and questions considered in the 2008 recommendations.

For this 2012 update, the working group used a modified Delphi process and obtained consensus (defined as $\geq 70\%$ agreement) from the CEP for inclusion of relevant clinical scenarios based on 1) review of each of the previous 2008 scenarios and 2) review of newly developed scenarios to address switching between therapies. The working group provided CEP members with manuscript abstracts and requested full-text articles to help inform decisions.

The CEP members also recommended the following: 1) use of the Food and Drug Administration (FDA) definitions of "serious" and "non-serious" adverse events, 2) exclusion of 3 disease-modifying antirheumatic drugs (DMARDs) used very infrequently (i.e., cyclosporine, azathioprine, and gold; see the original guideline document) or without additional relevant new data, and 3) exclusion of 1 biologic agent without additional relevant new evidence and with infrequent use (anakinra).

Rating the Appropriateness of Clinical Scenarios by the TFP

The TFP is referred to as the "panel". For the first round of ratings the guideline developer contacted the working group members by e-mail and provided them with the evidence report, clinical scenarios, and rating instructions. The developer asked them to use the evidence report and their clinical judgment to rate the "appropriateness" of the clinical scenarios under consideration. The panelists individually rated each scenario permutation using a 9-point Likert appropriateness scale. A median score of 1 to 3 indicated "not appropriate" and 7 to 9 indicated "appropriate" for taking action defined in the scenario. For all eventual recommendations, the RAND/UCLA appropriateness panel score required a median rating of 7 to 9. Those scenario permutations with median ratings in the 4 to 6 range and those with disagreement among the panelists (i.e., one-third or more TFP members rating the scenario in the 1 to 3 range and one-third or more rating it in the 7 to 9 range) were classified as "uncertain." At a face-to-face meeting with both the TFP and the CEP members on November 15, 2010, the anonymous first round of ratings by the panel, including dispersion of the scores, ranges, and median scores, was provided to the task force panelists.

The task force panelists agreed upon certain assumptions and qualifying statements on which they based their discussion and subsequent ratings of the scenarios (see Table 2 in the original guideline document). A second round of ratings by panel members occurred after extensive in-person discussion of the prior ratings and review of the evidence supporting each scenario.

Conversion of Clinical Scenarios to ACR RA Treatment Recommendations

After the TFP meeting was complete, recommendations were derived from directly transcribing the final clinical scenario ratings. Based on the ratings, scenario permutations were collapsed to yield the most parsimonious recommendations. For example, when ratings favored a drug indication for both moderate and high disease activity, one recommendation was given, specifying "moderate or high disease activity." In most circumstances, the recommendations included only positive and not negative statements. For example, the recommendations focused on when to initiate specific therapies rather than when an alternate therapy should not be used. Most of the recommendations were formulated by drug category (DMARD, anti-TNF biologic, non-TNF biologic listed alphabetically within category), since in many instances, the ratings were similar for medications within a drug category. The guideline developer specifically notes instances where a particular medication was recommended but others in its group were not endorsed. Two additional community-based rheumatologists independently reviewed the manuscript and provided

comments. CEP and TFP members reviewed and approved all final recommendations.

For each final recommendation, the strength of evidence was assigned using the methods from the American College of Cardiology (see the "Rating Scheme for the Strength of the Evidence" field). The evidence was rated by 4 panel experts (where each rated half of the evidence), and discrepancies were resolved by consensus.

Since many recommendations had multiple components (in most cases, multiple medication options), a range is sometimes provided for the level of evidence; for others, the level of evidence is provided following each recommendation.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

American College of Rheumatology (ACR) Peer Review of Recommendations

Following construction of the recommendations, the manuscript was reviewed through the regular journal review process and by more than 30 ACR members serving on the ACR Guidelines Subcommittee, ACR Quality of Care Committee, and ACR Board of Directors.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Appropriate use of disease-modifying antirheumatic drugs and biologic agents for the treatment of rheumatoid arthritis (RA), including switching between drugs
- Appropriate screening for tuberculosis reactivation, immunization, and treatment of RA patients with hepatitis, congestive heart failure, and/or malignancy

Potential Harms

Adverse effects of disease-modifying antirheumatic drugs (DMARDs) and biologic agents

Qualifying Statements

Qualifying Statements

- Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide guidance for particular patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to these guidelines and recommendations to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes but cannot guarantee any specific outcome. Guidelines and recommendations developed or endorsed by the ACR are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice.
- Therapies that were approved after the original literature review are not included in these recommendations.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

Foreign Language Translations

Patient Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, Moreland LW, O'Dell J, Winthrop KL, Beukelman T, Bridges SL Jr, Chatham WW, Paulus HE, Suarez-Almazor M, Bombardier C, Dougados M, Khanna D, King CM, Leong AL, Matteson EL, Schousboe JT, Moynihan E, Kolba KS, Jain A, Volkman ER, Agrawal H, Bae S, Mudano AS, Patkar NM, Saag KG. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2012 May;64(5):625-39. [45 references] [PubMed](#)

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2008 Jun 15 (revised 2012 May)

Guideline Developer(s)

American College of Rheumatology - Medical Specialty Society

Source(s) of Funding

American College of Rheumatology (ACR)

Guideline Committee

Core Expert Panel/Task Force Panel

Composition of Group That Authored the Guideline

Panel Members: Jasvinder A. Singh, MBBS, MPH, University of Alabama at Birmingham; Daniel E. Furst, MD, University of California, Los Angeles; Aseem Bharat, MBBS, MPH, University of Alabama at Birmingham; Jeffrey R. Curtis, MD, MPH, University of Alabama at Birmingham; Arthur F. Kavanaugh, MD, University of California, San Diego; Joel M. Kremer, MD, Albany Medical College, Albany, New York; Larry W. Moreland, MD, University of Pittsburgh, Pittsburgh, Pennsylvania; James O'Dell, MD, University of Nebraska, Omaha; Kevin L. Winthrop, MD, MPH, Oregon Health and Science University, Portland; Timothy Beukelman, MD, MSCE, University of Alabama at Birmingham; S. Louis Bridges Jr., MD, PhD, University of Alabama at Birmingham; W. Winn Chatham, MD, University of Alabama at Birmingham; Harold E. Paulus, MD, University of California, Los Angeles; Maria Suarez-Almazor, MD, MPH, University of Texas MD Anderson Cancer Center, Houston; Claire Bombardier, MD, MSc, Toronto General Research Institute, Toronto, Ontario, Canada; Maxime Dougados, MD, Hopital Cochin, Paris, France; Dinesh Khanna, MD, MSc, University of Michigan, Ann Arbor; Charles M. King, MD, North Mississippi Medical Center, Tupelo; Amye L. Leong, MBA, Healthy Motivation, Santa Barbara, California; Eric L. Matteson, MD, MPH, Mayo Clinic, Rochester, Minnesota; John T. Schousboe, MD, PhD, University of Minnesota and Park Nicollet Clinic, Minneapolis; Eileen Moynihan, MD, Highmark Medicare Services, Woodbury, New Jersey; Karen S. Kolba, MD, Pacific Arthritis Center, Santa Maria, California; Archana Jain, MD, University of Alabama at Birmingham; Elizabeth R. Volkman, MD, University of California, Los Angeles; Harsh Agrawal, MD, University of California, Los Angeles; Sangmee Bae, BS, University of California, Los Angeles; Amy S. Mudano, MPH, University of Alabama at Birmingham; Nivedita M. Patkar, MD, MSPH, University of Alabama at Birmingham; Kenneth G. Saag, MD, MSc, University of Alabama at Birmingham

Financial Disclosures/Conflicts of Interest

Dr. Singh has received consultant fees, speaking fees, and/or honoraria (less than \$10,000 each) from Allergan, Ardea, Savient, and Novartis, and (more than \$10,000) from Takeda, has received an investigator-initiated grant from Savient and Takeda, and is an executive member of an international organization, Outcome Measures in Rheumatology (OMERACT). Dr. Furst has received consultant fees, speaking fees, and/or honoraria (less than \$10,000 each) from Abbott, Actelion, Amgen, BMS, Biogen Idec, UCB, Gilead, Centocor, GSK, Novartis, Pfizer, NIH, and

Roche/Genentech, and is a member of the Consortium of Rheumatology Researchers of North America (CORRONA). Dr. Curtis has received consultant fees, speaking fees, and/or honoraria (less than \$10,000 each) from Pfizer, BMS, Crescendo, and Abbott, and (more than \$10,000 each) from Roche, Genentech, UCB, Centocor, CORRONA, and Amgen. Dr. Kavanaugh has conducted clinical research for Centocor, UCB, Genentech/Roche, NIH, Abbott, Takeda, and Amgen. Dr. Kremer has received consultant fees, speaking fees, and/or honoraria (less than \$10,000 each) from Pfizer, BMS, and Amgen, and (more than \$10,000) from Genentech. Dr. Moreland has received consultant fees (less than \$10,000) from Pfizer and is a member of the data safety monitoring board for ChemoCentryx. Dr. Winthrop has received consultant fees, speaking fees, and/or honoraria (less than \$10,000 each) from Abbott, Amgen, Pfizer, Cellectis, and Wyeth. Dr. Chatham has served as a paid consultant with investment analysts on behalf of Gerson Lehman and Leerink-Swann. Dr. Bombardier has received honoraria (less than \$10,000 each) and/or served on the advisory board for Abbott Canada, AstraZeneca, Biogen Idec, BMS, Pfizer (Wyeth), Merck (Schering), Janssen (Merck), and Takeda, and has received honoraria (more than \$10,000 each) from Abbott International and Pfizer. Dr. Dougados has received consultant fees, speaking fees, and/or honoraria (less than \$10,000 each) from Pfizer, Abbott, UCB, BMS, and Roche. Dr. Khanna has received consultant fees, speaking fees, and/or honoraria (less than \$10,000 each) from Genentech, UCB, Pfizer, Actelion, and Gilead. Ms Leong has received consultant fees, speaking fees, and/or honoraria (more than \$10,000 each) from Centocor Ortho Biotech and GlaxoSmithKline. Dr. Kolba owns stock and/or stock options in Merck, Amgen, and Genentech. Dr. Saag has received consultant fees, speaking fees, and/or honoraria (less than \$10,000 each) from Merck, Lilly, Novartis, Genentech, Horizon, and URL, and (more than \$10,000) from Amgen.

Guideline Status

Note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary.

Guideline Availability

The updated guideline is available from the [American College of Rheumatology Web site](#) .

Availability of Companion Documents

None available

Patient Resources

The following are available:

- Abatacept (*Orencia*). 2012 Jul. 3 p. Available in Portable Document Format (PDF) from the [American College of Rheumatology \(ACR\) Web site](#) .
- Anti-TNF. 2012 Jun. 5 p. Available in PDF from the [ACR Web site](#) .
- Cyclosporine (*Neoral*, *Sandimmune*, *Gengraf*). 2012 Apr. 3 p. Available in PDF from the [ACR Web site](#) .
- Gold preparations (*Myochrysine*, *Ridaura*, *Solganol*). 2012 May. 3 p. Available in PDF from the [ACR Web site](#) .
- Hydroxychloroquine (*Plaquenil*). 3 p. 2012 Apr. Available in PDF from the [ACR Web site](#) .
- Leflunomide (*Arava*). 2012 Apr. 3 p. Available in PDF from the [ACR Web site](#) .
- Methotrexate (*Rheumatrex*, *Trexall*). 2012 May. 3 p. Available in PDF from the [ACR Web site](#) .
- Minocycline (*Minocin*). 2012 May. 3 p. Available in PDF from the [ACR Web site](#) .
- Rituximab (*Rituxan* and *MabThera*). 2012 Feb. 3 p. Available in PDF from the [ACR Web site](#) .
- Sulfasalazine (*Azulfidine*). 2012 May. 3 p. Available in PDF from the [ACR Web site](#) .
- Rheumatoid arthritis. 2011 Dec. 5 p. Available in PDF in [English](#) and [Spanish](#) from the ACR Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This summary was completed by ECRI Institute on June 29, 2011. The information was verified by the guideline developer on July 25, 2011. This summary was updated by ECRI Institute on October 12, 2011 following the U.S. Food and Drug Administration (FDA) advisory on Tumor Necrosis Factor-alpha (TNF α) Blockers. This NGC summary was updated by ECRI Institute on July 31, 2012. The updated information was verified by the guideline developer on August 24, 2012. This summary was updated by ECRI Institute on November 21, 2013 following the U.S. Food and Drug Administration advisory on Arzerra (ofatumumab) and Rituxan (rituximab).

Copyright Statement

This NGC summary is based on the original guideline, which is subject to the guideline developer's copyright restrictions.

Disclaimer

NGC Disclaimer

The National Guideline Clearinghouse^{â„¢} (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the [NGC Inclusion Criteria](#).

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.